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Historical Overview of Pharmacognosy and Phytochemistry

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1.1 Introduction to Pharmacognosy

Pharmacognosy is derived from two Greek words that mean "drug" and "knowledge." Pharmacognosy is the study of natural medications derived from organisms, such as plants, microorganisms, and animals, and this term evolved autonomously, consistent with circumstances, and lasted in such form until the twentieth century. However, at the end of World War II, the discovery and acquisition of penicillin demonstrated that separation and structural analysis procedures, as well as pharmacognosy, were moving forward together [1].

Many significant medications, such as morphine, atropine, galantamine, and others, have originated from natural sources and continue to serve as good model molecules in drug development. The American Society of Pharmacognosy defines pharmacognosy as "the study of natural product molecules (typically secondary metabolites) that are useful for their medicinal, ecological, gustatory, or other functional properties" [2]. To assess the current validity of pharmacognosy as an academic and practical field, it is required to name the fields included in pharmacognosy, either fully or partially, drawing on a wide range of biological and chemical disciplines, such as botany, ethnobotany, marine biology, microbiology, herbal medicine, chemistry, biotechnology, phytochemistry, pharmacology, pharmaceutics, clinical pharmacy, and pharmacy practice. Other fields, such as the technical disciplines, were also included in pharmacognosy, including cataloging and classification of natural raw materials and computer methods like chemical docking [1]. It is worth mentioning that pharmacognosy, in conjunction with contemporary medicine, can create safe and effective medications, and according to a recent World Health Organization (WHO) survey, around 80% of the world's population still uses natural products for their main healthcare requirements [3].

Traditional medicine is also a branch of pharmacognosy, and most developing nations still rely on herbal treatments. As a result, pharmacognosy remains popular in the pharmaceutical sciences and plays vital role in drug discovery [4].

1.2 Historical Development of Pharmacognosy

The term "pharmacognosy" was introduced by the Australian physician Schmidt in 1811, and then in 1815, the Polish pharmacist Enoteus Sedler used it in his work "*Analecta Pharmacognostica*." Before that time, the expression was intended for the first time in Materia Medica, which was written by a Viennese pharmacist, Adam Smith (1759–1809) [5]. Additionally, there are other names at the present time for this scientific discipline in the entire world [6, 7]. The history of pharmacognosy represents the history of pharmacy and medicine. In each culture, a group of people developed skills in collecting, testing, and employing therapeutic plants to treat ailments; this corresponds to the basis for the concepts of herbal medicine and folk therapy, which have a history as old as human civilization and have been used in medicinal activities since antiquity as the primary remedies in the traditional system of medicine [8]. The early medicines of the Pharaohs, the Chinese, the Greeks, and the Romans described many therapeutic plants, while Arab physicians (Rhazes 865–925; Avicenna 980–1037) depended heavily on plants for therapy [3].

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1.2.1 Mesopotamia Region

Around 5000 years ago, the first documented evidence of medicinal plant use in medication manufacture was discovered on a Sumerian clay slab. It contained 12 medicine preparation techniques based on more than 250 distinct botanicals [9].

1.2.2 China

According to mythology, Chinese pharmacy began with Shen Nung (about 2700 BC), an emperor who sought out and examined the medicinal properties of several hundred herbs. He claimed to have tested many of them on himself and to have penned the first Pen T-Sao, or Native Herbal, in which 365 medications were recorded. These were categorized into the following categories: 120 emperor herbs of high, food-grade quality that are nontoxic and could be taken in large quantities to maintain health over time; 120 minister herbs, some mildly toxic and some not, with stronger therapeutic action to heal diseases; and 125 servant herbs with definite action to treat disease and eliminate stagnation. Because most of those in the last group are poisonous, they should not be used on a daily basis for weeks or months. Shen Nung has investigated several herbs, barks, and roots gathered from fields, marshes, and woodlands that are still used in pharmacy, such as stramonium, podophyllum, ginseng, rhubarb, ephedra, and cinnamon bark [10, 11].

1.2.3 India

The usage of ancient traditional medicines like Siddha, Buddha, Ayurveda, and Unani medicine for treatment is well known in India. These therapeutic methods are also mentioned in the Vedas and other ancient writings and traditions. The *Vedas,* India's holy books, recommend herbal medicine, which is rich in that region. India is home to a variety of spice plants, including nutmeg, pepper, and clove [12].

Between 500 and 2500 BC, Ayurveda evolved and prospered throughout India. The original definition of Ayurveda was "science of life," because the ancient Indian system of health care focused on human perspectives and illness. It has been acknowledged that pleasant health implies metabolically well-balanced humans [13].

1.2.4 Ancient Egypt

The *Ebers Papyrus* is an Egyptian medical papyrus that is considered to be one of the earliest and most important medical papyri of ancient Egypt. It was composed around 1550 BC and includes 800 prescriptions for 700 plant species and drugs used in therapy, such as pomegranate, castor oil plant, aloe, senna, coriander, onion, centaury, fig, willow, juniper, garlic, common, and others. A priest, a doctor, and a pharmacist who prescribed medications healed sick patients. [14].

1.2.5 The Greeks

Hippocrates' books (459–370 BC) contain 300 therapeutic herbs classified by physiological activity [15]. Theophrastus (371–287 BC), known as "the father of botany," established botanical science and made great contributions to the categorization and description of therapeutic plants with his writings "*De Causis Plantarum*" (Plant Etiology) and "*De Historia Plantarum*" (Plant History). In his books, he created a categorization of over 500 medicinal plants known at the time and emphasized the use of herbal plants by gradually increasing the doses [16].

While Dioscorides, known as "the father of pharmacognosy," was a military physician and pharmacognosist in Nero's Army, investigated medicinal plants wherever he traveled with the Roman Army. Around the year 77 AD, he published "De Materia Medica." This well-known ancient history book, which has been translated multiple times, contains a wealth of knowledge about the therapeutic herbs that were the core of Materia Medica until the late Middle Ages and later [17]. Of the 944 medications detailed, 657 are of plant origin, with details of the outer appearance, locality, mode of collection, production of the medicinal formulations, and therapeutic effect. In addition to the plant description, the names in various languages and the locations where they are grown are mentioned. Galen (131–200 AD), the most distinguished Roman Greek physician of the time, created the first list of drugs having comparable or identical activity. He also introduced into medicine various novel plant remedies that Dioscorides had not previously documented [10, 18].

1.2.6 Arabic and Islamic Region

The period from the eighth to the fifteenth centuries was known as the Golden Age of Arabic Medicine, due to numerous innovations and significant successes in the fields of medicine and pharmacy achieved by noticeable Arabic scientists, such as Hunayn bin Ishaq, Yuhann Ibn Masawayh, Ali Ibn Sahl at-Taberi, Sabur bin Sahl, ibn Zakarya al-Razi, Rabbi Moses bin Maimon, Ali ibn Abbas al-Majusi, Abul Kasim al-Zahrawi, Ibn Jazlah, Ibn Sina, Ibn al-Tilmidh, Ibn al-Baitar, Kohen al Baitar, Abu ar-Rayhan al-Biruni, Ibn al-Nafis, and others [19, 20].

During the Middle Ages, around 1000 medicinal plants were recorded in the Arab texts "*De Re Medica*" by John Mesue (850 AD), "Canon Medicinae" by Avicenna (980–1037), and "Liber Magnae Collectionis Simplicum

Alimentorum Et Medicamentorum" by Ibn Baitar [10]. The Arabs should be credited for greatly enhancing Materia Medica. They also invented several staining agents and were the first to use tannins. Some Arab medicines are still utilized today, though in a different manner [21].

1.3 Development of Pharmacognosy in the Modern Era

In the eighteenth century, Linnaeus (1707–1788), the Swedish botanist, presented a concise description and classification of the species described up to that point in his work, *Species Plantarum* (1753). The species were described and named regardless of whether or not some of them had previously been identified elsewhere. For naming, a polynomial method was utilized, with the first word indicating the genus and the rest of the polynomial phrase outlining various features of the plant. Linnaeus altered the naming system to make it binominal. The genus name (with an initial capital letter) and the species name (with an initial small letter) were combined to form the name of each species [22].

The nineteenth century noted the birth of scientific pharmacy and was a turning point in the understanding and application of therapeutic herbs with the advancement of chemical procedures and the discovery, substantiation, and isolation of alkaloids, glycosides, tannins, saponosides, etheric oils, vitamins, morphine, hormones, and other active chemicals from medicinal plants [10, 23]. Modern pharmacognosy emerged between 1934 and 1960; this development was mostly as a result of events as follows:

- Discovery of penicillin in 1982
- The isolation of reserpine in 1952
- The study of *Vinca rosea* anticancer activity
- The preparation of semi-steroidal hormones

Pure therapies, alkaloids, and glycosides were rapidly replacing the medications from which they had been extracted. Nonetheless, it was quickly discovered that, while pure alkaloids had a rapid impact, alkaloid medicines had a more complete and long-lasting effect. In the early twentieth century, methods for stabilizing fresh medicinal plants, particularly those having labile medicinal components, were proposed. Furthermore, much effort was devoted to researching production conditions [24]. Between 1971 and 1990, novel drugs, such as teniposide, octoposide, E- and Z-guggulsterone, nebulon, artemisinin, and plonotol were released all around the world. From 1991 to 1995, approximately 2% of medications were launched, including paclitaxel, irinotecan, topotecan, and others [3].

1.4 The Relevance of Pharmacognosy in Pharmacological Research on Herbal Medicinal Products

Herbal medicine products must be secure, safe, efficient, and of standard quality, just like all other medications. However, laws governing the use of herbal medicines vary from one country to another, and herbal preparations are sometimes used in less strictly controlled product categories like dietary supplements in addition to being used as medicines. As a result, consumers sometimes find it difficult to distinguish between high-quality and low-quality goods. However, compared to conventional pharmaceuticals, herbal medicines have several unique qualities.

Because of plants' characteristic variability and a wide range of outside influences, they are complex multicomponent mixtures whose phytochemical constituents are not constant. Consequently, it is essential to closely monitor the entire process of production of herbal medicines.

To begin with, the medicinal plant raw materials must be accurately authenticated and free of adulterants and contaminants. Plant metabolite production is strongly influenced by a variety of factors during plant growth, including temperature, humidity, developmental stage, harvest season, and time. The phytochemical components of herbal material can also be significantly changed by postharvest processing procedures like drying and storage. Like many phytopharmaceutical production processes, the extraction solvent, requirements, and stages must be optimized to enrich the bioactive constituents in the extract of medicinal herbs [25]. As a result, appropriate quality assessment measures should be used in conjunction with every step of production. Various techniques must be used depending on this task, including macroscopic, microscopic, and DNA-based authentication techniques followed by phytochemical techniques, including chromatographic analysis, such as gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS).

1.5 Taxonomy and Botanical Authenticity

In previous years, following a few fundamental guidelines for suitable documentation even during the plant collection stage was the first step in the authentication process. Documented information on the collected (obtained) plant specimen should include the Latin binomial name, the common name, an indication of the collected plant part(s), the name of the person who collected it (collector), the GPS position and geographical description of the collection site,

a unique collection number, a digital picture of the plant before and after harvest, and information on performed postharvest processing steps (drying method, time, and temperature) [26]. As authentication in the first instance involves the comparison of the herbal starting material with authentic reference samples, it was necessary to collect several plant voucher specimens (ideally from different phenological stages, e.g. vegetative, flowering, and fruiting) and to deposit them either in a registered public herbarium, in a certified research institute, or, in the case of commercial materials, in an on-site herbarium repository [27]. Plant taxonomical authentication has three main objectives: identification, nomenclature, and classification.

1.5.1 Plant Identification

It is a process of assigning plants to a specified group. The identification could be completed by using natural key systems using morphological characters that could be compared with known databases, "books of *flora*," by a professional taxonomist, and then by comparison with voucher specimens to achieve the plants' genus. Once a plant specimen has been identified, its name and properties are known. Misidentification of medicinal plants occurs inadvertently either at the plant collection site or at the drying stage of the herbal material, for example, when an importer or retailer confuses one herb with another due to incorrect labeling or similar appearance. Accordingly, documentation of medicinal plants should be based on accepted classification systems, scientific literature, and publications.

Botanical microscopic authentication has long been used to authenticate herbal products in several countries, as recorded in various pharmacopeias, to detect the adulteration and substitution of medicinal plants. It is because of its advantages: a slight quantity of needed samples, low costs, speed, simplicity, and reliability [28]. In addition, herbal pharmacopeia monographs usually contain a detailed microscopic drug description, allowing a first assessment of identity and, in some cases, the identification of common adulterated drugs [25]. For example, *Azadirachta indica* A. Juss. (neem), a traditional herbal species of importance, widely used plant for the treatment of numerous diseases, was adulterated with the closely related botanical species *Melia azedarach* L. The lateral was commercially marketed under the same trade name of neem and belonged to the same family, Meliaceae. Authentication, adulteration, and standardization of this herbal medicine were achieved using the macroscopic and microscopic morphological investigation of leaves, ultraviolet (UV) and infrared (IR) analyses, as well as scanning electron microscope (SEM) of pollen investigation [29].

1.5.2 Plant Nomenclature

Each plant should have two parts which are known by binomial name and follow the roles of ICBN (International Code of Botanical Nomenclature). The intent of the code is that each taxonomic group (taxon) of plants has only one accepted name that is approved worldwide, providing that it has the same position circumscription, and rank. The binomial name should be printed in an italic font style; for example, *Rorippa palustris* L. When handwritten, a binomial name should be underlined; for example, *Rorippa palustris* L. The first part of the binomial, the genus name, was always written with an initial capital letter, while the second part was written with an initial small letter. The binomial name was usually followed by the "authority"; a way of defining the scientist who published the name. For example, *Posidonia oceanica* L. "L." is an abbreviation for the author named this species "Linnaeus." When the original name is changed, for example, the species was moved to a different genus; it was used two brackets around the original author and specifies the author who made the change. For example, *Kickxia aegyptiaca* (L.) Nábělek, where "L." is the author who first named this species as *Antirrhinum aegyptiacum* L., and then "Nábělek" transferred it to the genus *Kickxia*.

Frequently, for medicinal plants, not only the scientific Latin name is in use, but there are also pharmacopeial names, local names, vernacular names, English names, etc. Consequently, only authorized scientific names should be used to evade confusion. Aside from confusing nomenclature, the misidentification could be caused by the similar appearance of herbal material, accompanied by misperception regarding historical records and local customs. Therefore, a careful study of ancient literature, together with modern analytical techniques, is often required to properly authenticate herbal material [25].

1.5.3 Plant Classification

Plant classification is placing known plants into categories or groups to show some relationship. A systematic classification follows a scheme of rules that standardizes the results, and groups successive categories into a hierarchy. The ICBN recognized seven main ranks in the hierarchy, where the ending of the name indicates its rank (Table 1.1).

Botanical identification was carried out by examining the whole plant specimen after collection by comparison with ideally authenticated reference models. Macroscopic identification concerns the assessment of macromorphological

characteristics of fresh, dried, or sliced mass of medicinal plant material [30]. Macromorphological characters depend on the variations of the external features of both vegetative (leaves, stems, and roots) (Figure 1.1) and reproductive organs (inflorescence, flowers, seeds, and fruits) (Figure 1.2) both sorts are found in all plants. Morphological features are simply observed, and discovery applied use in the descriptions and keys more than any other taxonomic features. Macromorphological authentication often also requires access to herbarium voucher specimens. Micromorphological investigation was a general term for studying the internal structure of plants. Although the macromorphological differences of closely related species are often so difficult to distinguish, any further characteristic feature may be welcomed, even though it involves the cutting of a section and its examination under the microscope. The microscopic investigation could be subjected to fresh or dry plant material as whole, fragmented, or powdered. The macro-and microscopic methods are very widely applied for the authentication persistence of traditional herbs as they are very time- and cost-effective [31]. Furthermore, several specified illustrated textbooks on macroscopic and microscopic descriptions of the most used medicinal plants are accessible [25].

Table 1.1 The hierarchy of taxonomic ranks. Example shows the classification of *Crocus sativus* L. (Saffron).

Rank	Ending	Example
Kingdom	various	Plantae
Division or Phylum	---phyta	Magnoliophyta
Class	---opsida	Liliopsida
Order	---ales	Asparagales
Family	---aceae	Iridaceae
Genus	*various*	*Crocus*
Species	*various*	*Crocus sativus* L.

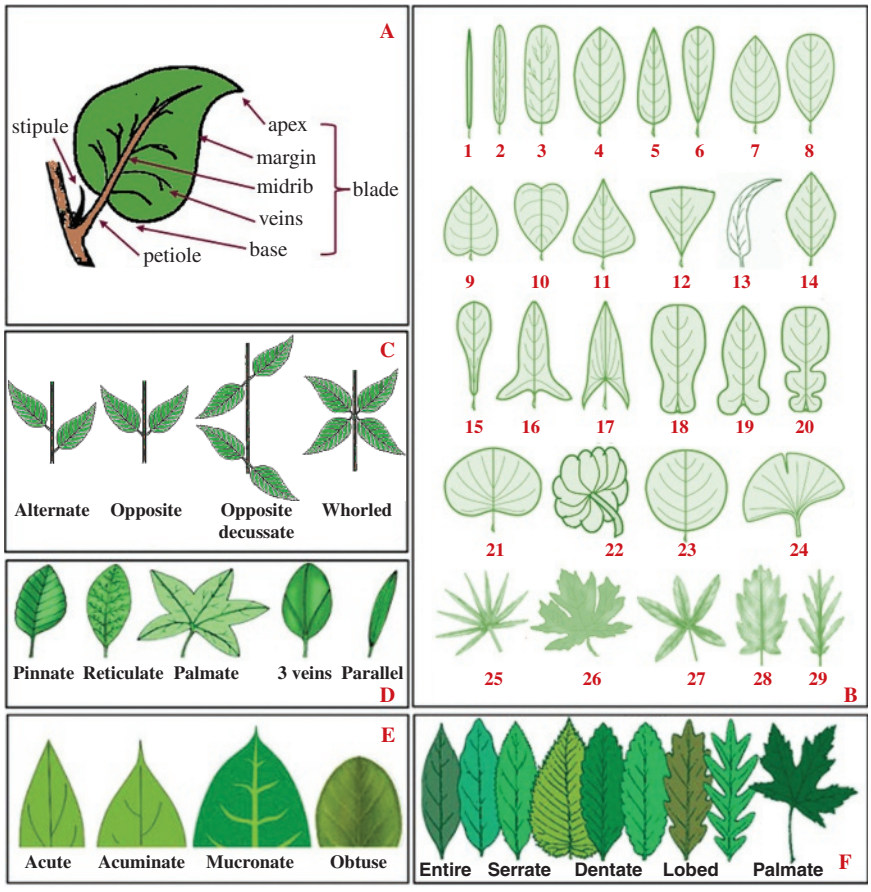


Figure 1.1 Vegetative morphology (leaf): (a) leaf structure, (b) leaf shapes; 1: acicular; 2: linear; 3: oblong; 4: elliptic; 5: lanceolate; 6: oblanceolate; 7: ovate; 8: obovate; 9: cordate; 10: obcordate; 11: deltoid; 12: obdeltoid; 13: cuneate; 14: rhomboid; 15: reniform; 16: peltate; 17: orbicular; 18: spathulate; 19: hastate; 20: sagittate; 21: lunate; 22: pandurate; 23: flabellate; 24: fan-shaped; 25: subulate; 26: palmatifid; 27: palmatisect; 28: pinnatifid; and 29: pinnatisect, (c) leaf arrangement, (d) leaf venation, (e) leaf apex, and (f) leaf margin. *Source:* https://www.slideserve.com/alcina/plant-structure-macro

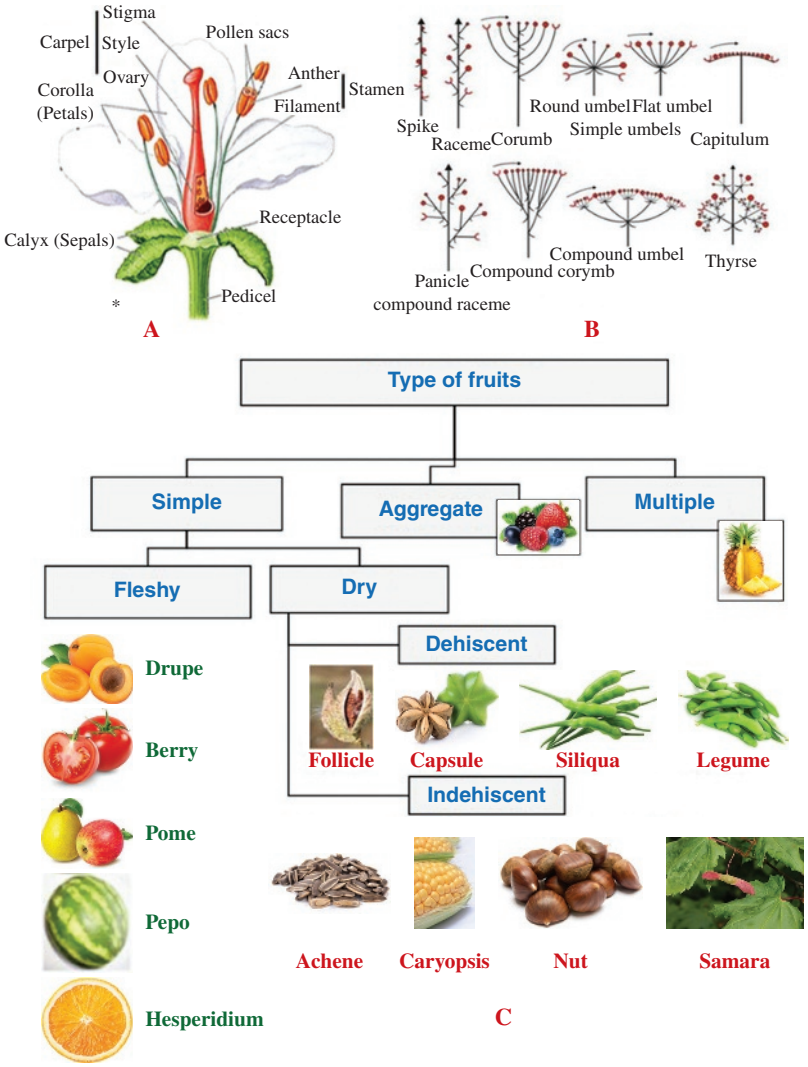


Figure 1.2 Reproductive morphology: (a) flower structure, (b) type of inflorescences, and (c) types of fruits. *Source:* https://meganbio11.weebly.com/plants.html

1.6 Phytochemistry – An Expanded Role in Traditional Medicine (History and Progress in Drug Discovery)

Phytochemistry has played a significant role in traditional medicine throughout history and continues to contribute to drug discovery efforts. Historically, the observations and knowledge passed down through generations formed the basis of traditional medicine. Ancient civilizations, such as the Egyptians, Mesopotamians, Greeks, and Chinese extensively documented the use of specific plants and plant preparations for medicinal purposes. This empirical knowledge laid the groundwork for the development of phytochemistry as a scientific discipline [32]. As well, herbalism, the use of plants for medicinal purposes, was prevalent in many cultures throughout history. Traditional medicine systems, such as Ayurveda in India, traditional Chinese medicine (TCM), Unani in the Middle East, and Indigenous healing practices worldwide, incorporated plant-based remedies into their healing modalities. These systems recognized the importance of specific plants and their active constituents in promoting health and treating diseases [33]. On the other hand, the scientific exploration of plant constituents began to emerge during the 19th century. Chemists and botanists started isolating and identifying active compounds from medicinal plants. For example, the isolation of morphine from opium poppy (*Papaver somniferum* L.) by Friedrich Sertürner in 1803 marked a significant milestone in the field of phytochemistry [34]. As scientific methodologies and techniques advanced, researchers began to identify and characterize the chemical constituents responsible for the therapeutic effects of medicinal plants. This led to the

discovery of various active compounds, including alkaloids, flavonoids, terpenoids, and phenolic compounds, among others. Consequently, the knowledge of medicinal plants and their active constituents was compiled into materia medica and pharmacopoeias. These texts provided guidelines for the identification, preparation, and usage of medicinal plants in traditional medicine systems. Examples include the Ayurvedic texts, the Chinese Pharmacopoeia, and the European Pharmacopoeia [35]. In the twentieth century, there was an increased emphasis on scientific validation and standardization of traditional medicine practices. Phytochemistry played a crucial role in this process by providing scientific evidence supporting the efficacy and safety of plant-based remedies, where active compounds were isolated, tested, and evaluated for their pharmacological activities and mechanisms of action [36]. Interestingly, with advancements in scientific research and technology, the integration of traditional medicine and phytochemistry with modern medicine became a focus of interest. Researchers started to bridge the gap between traditional knowledge and scientific understanding by exploring the potential of plant-derived compounds in drug discovery and development [37].

Today, the progress in drug discovery owes much to the contributions of phytochemistry. As scientists began to investigate the chemical constituents of medicinal plants, they discovered bioactive compounds responsible for the observed therapeutic effects. Isolating and characterizing these compounds allowed researchers to understand their structures, properties, and mechanisms of action. As well, scientific validation of the active constituents of traditionally used herbs enhances the credibility and acceptance of these traditional medicine systems. These bioactive compounds can serve as leads for the development of new drugs or be used as scaffolds for synthetic modifications to enhance their efficacy and safety [38]. One notable example is the discovery of the compound artemisinin from the sweet annie plant (*Artemisia annua* L.) used in TCM for treating malaria. Its discovery led to the development of artemisinin-based combination therapies (ACTs), which are now widely used as first-line treatments for malaria. Examples of ACTs include artemether/lumefantrine and artesunate/amodiaquine [39]. Similarly, quinine, originally isolated from the bark of the cinchona tree (*Cinchona* spp.), has been used for centuries to treat malaria. It is still used today in some cases of drug-resistant malaria, although it has been largely replaced by artemisinin-based therapies [40]. Also, vinblastine and vincristine are alkaloid compounds derived from the Madagascar periwinkle plant (*Catharanthus roseus* (L.) G. Don). These drugs have shown efficacy in treating various types of cancer, including Hodgkin's lymphoma, leukemia, and solid tumors [41]. Additionally, paclitaxel, originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia* Nutt.), is an important chemotherapeutic agent used in the treatment of breast, ovarian, and lung cancers. It inhibits cell division by stabilizing microtubules, leading to cell cycle arrest and apoptosis [42]. In addition, digoxin, derived from the foxglove plant (*Digitalis purpurea* L.), is used in the management of heart failure and certain cardiac arrhythmias. It works by inhibiting the sodium-potassium ATPase pump, leading to increased intracellular calcium levels and improved cardiac contractility [43]. Additionally, colchicine, derived from the autumn crocus plant (*Colchicum autumnale* L.), is used in the treatment of gout and other inflammatory conditions. It acts by inhibiting microtubule polymerization and reducing the migration of inflammatory cells [44]. Likewise, salicylates, including acetylsalicylic acid (aspirin), are derived from the bark of willow trees (*Salix* spp.). They have analgesic, anti-inflammatory, and antipyretic properties and are widely used as pain relievers and for their antiplatelet effects [45]. Additionally, curcumin, derived from the turmeric plant (*Curcuma longa* L.), has demonstrated anti-inflammatory and antioxidant properties and is being investigated for its neuroprotective effects in Alzheimer's disease [46]. Metformin, a widely used oral antidiabetic drug, was derived from the French lilac plant (*Galega officinalis* L.) [47]. Additionally, compounds such as berberine (found in various plants including *Berberis* spp.) and resveratrol (found in grapes and berries) have shown promise in improving insulin sensitivity and glucose metabolism [48]. Theophylline, a compound found in tea (*Camellia sinensis* (L.) Kuntze) and cocoa (*Theobroma cacao* L.), has been used in the treatment of asthma [49]. Also, the compound loperamide, derived from the opium poppy (*Papaver somniferum* L.), is an antidiarrheal medication used to relieve symptoms of acute diarrhea [50]. Silymarin, derived from milk thistle (*Silybum marianum* (L.) Gaertn.), has hepatoprotective properties and is used as a supportive therapy in liver diseases, such as hepatitis and cirrhosis [51].

These examples highlight the diverse range of diseases and conditions that have been targeted by drugs developed through phytochemistry. The exploration of natural products continues to provide insights into potential therapeutic options for various health conditions, and ongoing research in this field holds promise for future drug development.

1.7 Recent Progress in Pharmacognosy and Phytochemistry

The recent advancements in pharmacognosy and phytochemistry are contributing to the development of safer and more effective natural products, the discovery of novel therapeutic compounds, and the integration of traditional medicine with modern healthcare systems. The field continues

to evolve, driven by interdisciplinary collaborations, scientific research, technological advancements, and a deeper understanding of the potential of natural products for human health and well-being [52]. Here are some notable developments:

1.7.1 Bioactivity-guided Fractionation

Phytochemistry employs bioactivity-guided fractionation, a process that involves sequentially isolating and testing fractions of plant extracts to identify the specific components responsible for the observed bioactivity. This approach helps narrow down the search for active compounds and accelerates the discovery of lead compounds for drug development. This methodology is well-achieved by the advancements in phytochemical analysis techniques, such as chromatography [53].

1.7.2 Identification of Bioactive Compounds from Adulterants

Identification and authentication of natural compounds away from adulterants were processed by some sophisticated analytical techniques, such as mid-infrared spectroscopy (MIR), near-infrared spectroscopy (NIR), Raman spectrum (RS), terahertz time-domain spectroscopy (THz-TDS), and nuclear magnetic resonance (NMR) spectroscopy. Usually, chemometric analyses are subjected in combination with the appropriate evidence from the spectral data and thus allow discrimination of the investigated herbal species [54].

Vibrational spectroscopic techniques (MIR, NIR, and RS) measure vibrational energy levels linked to the chemical bonds sample. A shift in the molecular dipole moment during vibration yields the IR spectrum, whereas a shift in polarizability during vibration yields the RS. In IR and R, specific peaks and bands correspond to specific functional groups of the molecules found in the sample [55]. As a result, their existence can provide information about a sample's chemical character [25].

In recent years, NIR spectroscopy has been employed for process analysis and quality control in several industries due to its simplicity, speed, accuracy, and non-destructive nature [56]. The shorter NIR wavelengths have a deeper penetrating range than the MIR range. To gather details on the characteristics of the hydrogen-containing groups in compounds, NIR spectroscopy, which operates within the wavelength range of 800 to 2500 nm, primarily records the spectral bands that correspond to the molecular vibrations of hydrogen bonds (e.g. C–H, O–H, and N–H) [54]. For example, the NIR technique was created to detect adulterants, synthetic antidiabetic drugs in antidiabetic herbal medicines [56]. The approach utilized in this study was constructed and validated using 127 batches of herbal anti-diabetic species and four pure synthetic anti-diabetic pharmaceuticals (gliclazide, glibenclamide, metformin, and glimepiride).

Moreover, THz spectroscopy is a new and potent research tool that offers a wealth of knowledge on the physics, chemistry, and structure of materials and biomedicine due to its benefits, which are non-destructive, safe, and rapid. THz spectroscopy uses a portion of the electromagnetic spectrum that falls between the microwave and infrared areas, as opposed to traditional far-infrared spectroscopy. Biological molecules exhibit complicated molecular vibrations in the terahertz range, including rotations, hydrogen bonding, low-frequency bond vibrations, and van der Waals forces. Biomolecules may be successfully recognized using terahertz characteristic spectra, particularly when their chemical structures are comparable. For example, THz-TDS was utilized by Yin et al. [57] to identify and analyze 10 common flavonoids, such as apigenin, baicalein, naringenin, hesperetin, daidzein, genistein, puerarin, and gastrodin, quantitatively and qualitatively. These flavonoids were identified by their THz absorption spectra, which showed markedly distinct characteristic absorption peaks in the terahertz region while having comparable chemical structures. Furthermore, THz spectroscopy was used to identify three flavonol aglycones with comparable structures: myricetin, quercetin, and kaempferol [57].

Similarly, NMR spectroscopy has disadvantages as well, like high cost and potential unsuitability for some applications, yet it can precisely determine the structures of some bioactive molecules in crude plant extracts – without the requirement for sample preparation or chromatographic separation beforehand – by detecting and quantifying chemical interactions [25, 54]. Every molecule with at least one proton may be identified using proton NMR ^{1}(H NMR). Additionally, the quantity of protons providing a given signal is exactly proportional to the area beneath the proton signal. As a result, any plant components that are present in a combination at a suitable concentration may be identified, and information about their relative proportions can also be acquired. For example, NMR-based methods have been widely used for authentication and quality control purposes in medicinal plants [54]. These methods are frequently used in conjunction with chemometric analysis. Examples of applications of NMR-based methods include the differentiation of closely related species, the determination of synthetic drugs blended in medicinal plants [58], and the sourcing of herbal species according to various geographic origins or ages of cultivation.

Quantitative NMR (qNMR) approaches are also thought to be highly feasible for the quality control of herbal products because of the inherent quantitative information of NMR data. This is because qNMR methods allow for direct quantitative assessment from crude extracts without the need for time-consuming and costly chromatographic techniques,

authentic reference standards, as well as exhausting sample preparation [59]. The procedure itself is straightforward, repeatable, and has a high throughput capacity, even though it necessitates the use of expensive and advanced instrumental equipment by skilled workers [60].

^{1}H NMR spectra can identify hundreds of signals due to the high number of elements typically found in a crude plant extract. A significant amount of these signals overlap, which makes interpreting the data more difficult. The large dynamic range of metabolites found in plant extracts is another crucial factor to consider. Due to the strong correlation between signal intensity and metabolite concentration in ^{1}H NMR spectroscopy, highly abundant metabolites, such as bulk components or sugars can obscure smaller metabolites, making it difficult to identify them in a sample.

As well, the chromatographic methods that are most adaptable for the phytochemical examination of herbal substances include thin-layer chromatography (TLC), GC-MS, HPLC, and LC-MS. They may be used for several objectives, including quality control using fingerprints and markers, authentications, and the identification of different adulterants and pollutants in herbal medicines.

TLC offers several benefits for the quality control of herbal products: it generally only requires basic sample preparation, is relatively inexpensive, easy to use, adaptable, quick, and allows for high specificity and high sensitivity, for example, by employing compound-specific derivatization reagents. Many herbal pharmacopeia monographs use TLC as a standard technique, primarily for identification and purity analysis. High-performance TLC (HPTLC) is a more sophisticated form of TLC that uses computer-controlled equipment for automated sample application, automated plate development under controlled conditions, and electronic documentation. It uses stationary phases with higher resolution because of a smaller and more uniform particle size [25].

Given the volatile or semi-volatile properties of many natural bioactive compounds, GC-MS is a very practical method for producing high-quality fingerprint chromatograms and efficiently analyzing complicated biological materials on both qualitative and quantitative levels. Recently, GC-MS was used in combination with chemometric analysis to determine the adulteration of saffron (Iranian and Spanish) with related flower parts of safflower and calendula (marigold). Principle component analysis labeled 2-caren-10-al and safranal as distinguishing volatile indicators of saffron from its related flowers, which are enriched with β-caryophyllene, estragole, and eugenol [61] (Figure 1.3).

For HPLC, high pressure is applied to transport the mobile phase through columns packed with stationary phase to achieve separation of analytes. It is one of the most often used methods for herbal medicine analysis. It has great resolution, is simple to use, and offers good selectivity and sensitivity since it could be used with a variety of fixed phases and detectors.

The development of ultra-high pressure liquid chromatography (UHPLC) instruments in recent years has made it possible to significantly improve traditional HPLC methodology. UHPLC instruments can tolerate backpressures of up to 1000 bar, whereas traditional HPLC instruments cannot tolerate backpressures of more than 400 bar [62]. The fundamental idea behind UHPLC is that a smaller particle size in the stationary phase results in a greater plate count (separation efficiency), led to a much shorter analysis time, and a noticeably increased backpressure.

Simple detectors that can record chromatographic traces, but do not provide structural information, like UV absorbance, fluorescence, or electric light scattering (ELS)

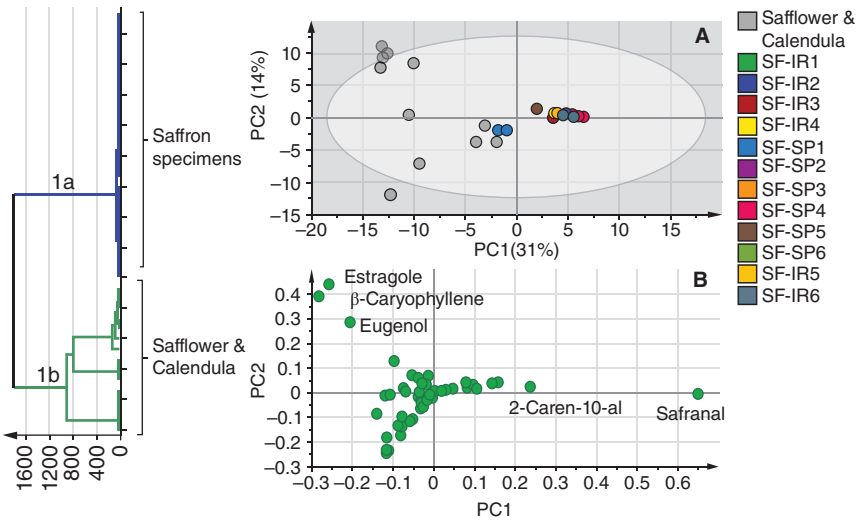
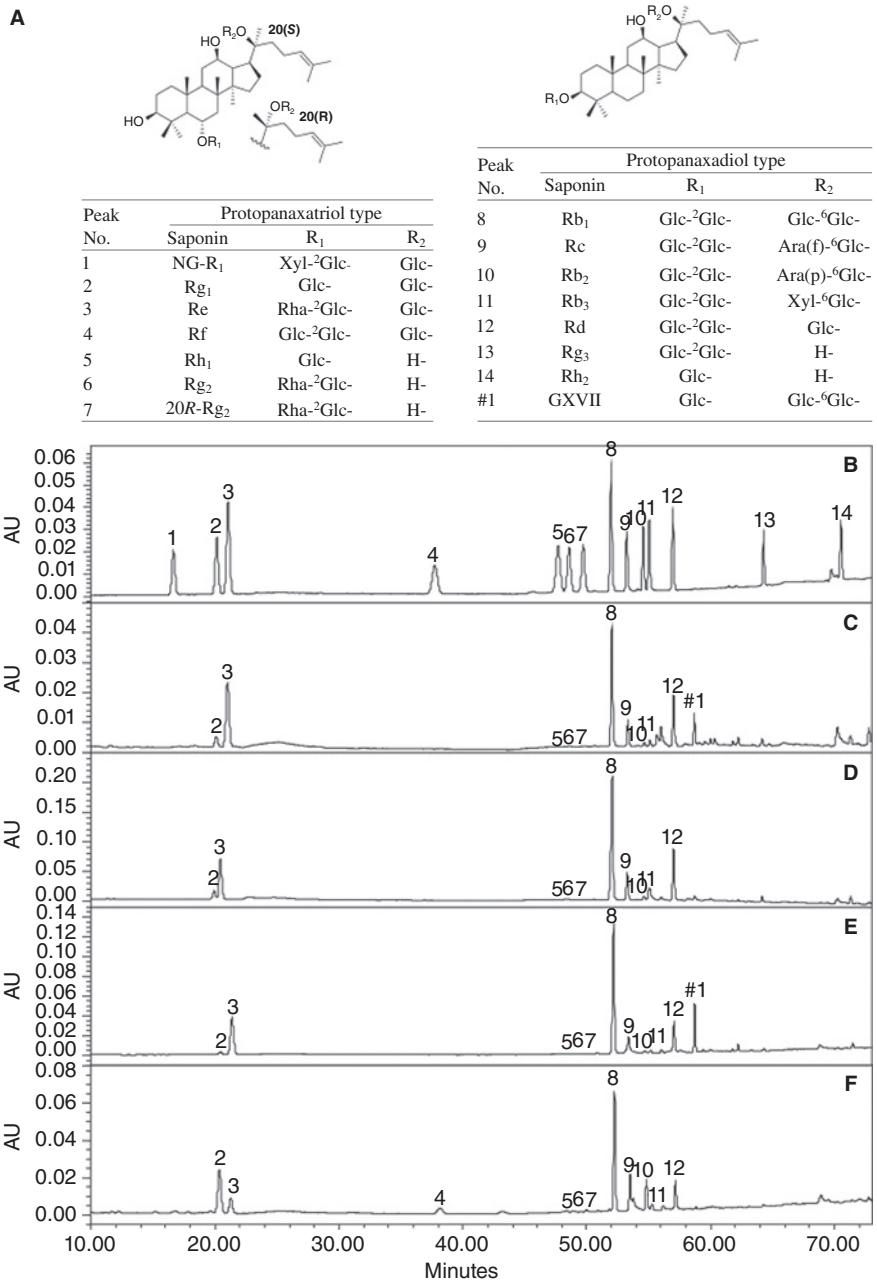


Figure 1.3 Principal component analysis (PCA) and hierarchical clustering of the extracted volatile constituents using solid-phase microextraction from saffron including Iranian saffron (SF-IR) and Spanish saffron (SF-SP) as well as from safflower and calendula flowers [61]: (a) Score plot of PC1 vs. PC2 scores. (b) Loading plot for PC1 & PC2 contributing volatiles and their assignments.

detectors, are only frequently used for standard quality control applications in the herbal industry. The UV absorbance detector is very suitable and sensitive in the case of compounds possessing chromophore groups, while fluorescent compounds can perceptively be detected by fluorescence detectors, as well as the ELS detector is reasonable for structures lacking chromophores or fluorescence. For example, HPLC combined with multivariate analyses has been used to improve quality assurance technology and identify adulterated products for American ginseng (*Panax quinquefolius* L.). Furthermore, this method was created to distinguish samples obtained from different cultivation regions (United States of America, Canada, and China) that cannot be compared to an adulterated commercial ginseng sample [63]. After further comparing their HPLC chromatograms, limited differences were found, e.g. gypenoside XVII was found significantly in samples of American ginseng grown in the United States of America and China, but not significantly in samples cultivated in Canada (Figure 1.4). Nevertheless, due to the high



Peak No.	Protopanaxatriol type		
	Saponin	R_1	R_2
1	NG-R_1	Xyl-^{2}Glc-	Glc-
2	Rg_1	Glc-	Glc-
3	Re	Rha-^{2}Glc-	Glc-
4	Rf	Glc-^{2}Glc-	Glc-
5	Rh_1	Glc-	H-
6	Rg_2	Rha-^{2}Glc-	H-
7	20*R*-Rg_2	Rha-^{2}Glc-	H-

Peak No.	Protopanaxadiol type		
	Saponin	R_1	R_2
8	Rb_1	Glc-^{2}Glc-	Glc-^{6}Glc-
9	Rc	Glc-^{2}Glc-	Ara(f)-^{6}Glc-
10	Rb_2	Glc-^{2}Glc-	Ara(p)-^{6}Glc-
11	Rb_3	Glc-^{2}Glc-	Xyl-^{6}Glc-
12	Rd	Glc-^{2}Glc-	Glc-
13	Rg_3	Glc-^{2}Glc-	H-
14	Rh_2	Glc-	H-
#1	GXVII	Glc-	Glc-^{6}Glc-

Figure 1.4 HPLC analysis of ginseng (*Panax quinquefolius* L.) samples. (a) Chemical structures of 14 tested ginsenoside saponins and GXVII (gypenoside XVII). HPLC chromatograms of (b) ginsenoside standards, (c) ginseng obtained from the United States of America, (d) ginseng obtained from Canada, (e) ginseng obtained from China, (f) an adulterated ginseng sample [63].

chromatographic similarity between samples from the three cultivation regions, the traditional HPLC fingerprint cannot be used to identify agricultural regions, so it is necessary to introduce a new method to achieve this goal [25].

Advanced detectors such as mass spectrometry or high-resolution mass spectrometry (HRMS) and diode array detection (DAD) record chromatographic traces and provide multidimensional data. These detection techniques are very helpful for creating information-rich chromatographic fingerprints for herbal traditional medications because of the structural information they offer. As an example, the processing of the UHPLC-DAD-HRMS study (positive mode) was performed to detect the modest quality and adulteration of *Ginkgo biloba* L. (Ginkgoaceae) leaf extracts or powders with extracts or powders of *Sophora japonica* L. (Fabaceae) fruits. The hydrolyzed *G. biloba* leaf extract, *S. japonica* fruit extract, and the standard compounds (genistein and apigenin) were analyzed. This method allows clear recognition of ginkgo adulterations with sophora, which is rich in genistein and its 4'-*O*-glucopyranoside (sophoricoside) as indicator compounds (both detected as genistein in the hydrolyzed extract) (Figure 1.5). The data stated that genistein could not be detected in any of the tested ginkgo samples, whereas traces of apigenin were detected instead [64].

1.7.3 Omics Approach

Metabolomics, the comprehensive analysis of small molecules in biological systems, has contributed to our understanding of the metabolic profile and chemical diversity of plants. Metabolite profiling techniques, such as metabolomic fingerprinting and metabolic pathway analysis, have revealed the complex chemical composition of plants and their potential therapeutic applications [65]. Genomics, transcriptomics, and proteomics have provided valuable insights into the biosynthesis pathways of bioactive compounds in plants. These omics approaches have facilitated the discovery of novel enzymes, genes, and regulatory mechanisms involved in the production of medicinal compounds [66].

1.7.4 Phytopharmacology and Mechanistic Studies

Pharmacological studies have focused on elucidating the mechanisms of action of bioactive compounds derived from medicinal plants. This includes investigating their interactions with biological targets, signaling pathways, and molecular mechanisms underlying their therapeutic effects. Such studies help validate the traditional use of medicinal plants and provide a scientific basis for their efficacy [67].

1.7.5 Multitargeted Approaches

Traditional pharmacognosy often involves the use of whole plant extracts or mixtures of compounds. Recent research has focused on understanding the synergistic interactions

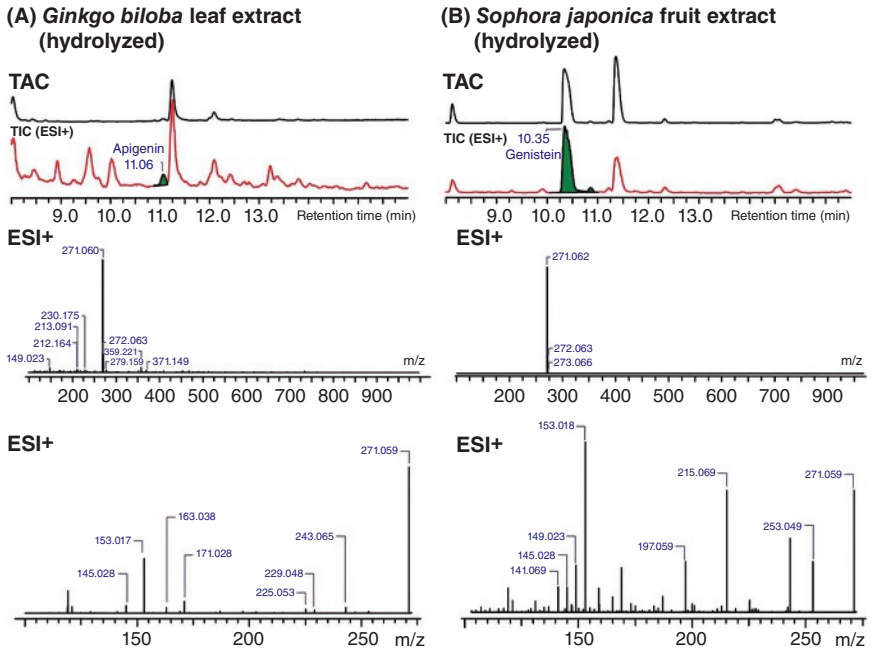


Figure 1.5 The total absorbance chromatograms and total ion chromatograms of hydrolyzed extract of (a) *Ginkgo biloba* leaf and *Sophora japonica* fruit (b) using UHPLC-DAD-HRMS analysis, in the positive ion mode, showed the authentication of apigenin and genistein, respectively, with their MS and MS2 spectra [64].

between multiple bioactive compounds within plant extracts. This multi-targeted approach recognizes that the therapeutic effects of medicinal plants may arise from the combined actions of several compounds, targeting multiple pathways or molecular targets simultaneously [68].

1.7.6 Bioavailability and Drug Delivery Systems

Enhancing the bioavailability and delivery of phytochemicals is a significant challenge in pharmacognosy. Researchers have made progress in developing novel drug delivery systems, such as nanoparticles, liposomes, and microencapsulation techniques, to improve the solubility, stability, and targeted delivery of phytochemicals [69].

1.7.7 Computational Approaches

Computational methods, including virtual screening, molecular docking, and predictive modeling, have gained prominence in phytochemistry. These techniques aid in the identification of potential bioactive compounds, target identification, and optimization of lead molecules. Computational approaches significantly expedite the drug discovery process and reduce the cost and time associated with experimental screening [70].

1.7.8 Standardization and Quality Control

Quality control measures have become increasingly important to ensure the safety and efficacy of herbal medicines. Pharmacognosy has made significant progress in developing standardized methods for the authentication, quality assessment, and standardization of herbal products. This includes the establishment of botanical reference standards, marker compound analysis, and the development of fingerprinting techniques [71]. DNA-based methods are an identically significant tool to accompany phytochemical approaches for medicinal plant authentication and to detect adulteration of herbal material with closely related species that are indistinguishable through their macro- and micro-morphological characteristics. DNA is a stable macromolecule that is not affected by extraneous factors or developmental stages and that is found in all plant tissues. DNA could be recovered from fresh and dried herbal material, and only small sample amounts are needed [72]. Frequent categories of DNA fingerprinting procedures have been established to assess DNA polymorphism for plant species authentication. Currently, most methods in use include polymerase chain reaction (PCR) for DNA amplification. Lately, DNA sequencing has been increasingly used either in amalgamation with or as a replacement for traditional DNA fingerprinting methods [73].

PCR-based DNA fingerprinting methods could be categorized based on the type of the selected genetic markers. Multilocus approaches use single oligonucleotide primers with random sequences to produce PCR fragments from genomic DNA. Multilocus systems include amplified fragment length polymorphism (AFLP), intersimple sequence repeat (ISSR), and random amplified polymorphic DNA (RAPD) techniques. In these methods, multilocus banding patterns are obtained after electrophoretic separation and do not require sequence information. In contrast, cleaved amplified polymorphic sequence (CAPS) is a combination of PCR of a defined sequence using specific primers and subsequent digestion with a restriction enzyme [25]. Therefore, it was formerly termed restriction fragment length polymorphism (PCR–RFLP). The digested fragments are separated into agarose gels. The sensitivity of the method is limited as DNA polymorphisms need to affect restriction sites to be detected. Likewise, CAPS markers can only be established where mutations interrupt or create a restriction enzyme recognition site. However, the PCR–RFLP method has been used for the certification of various herbal species.

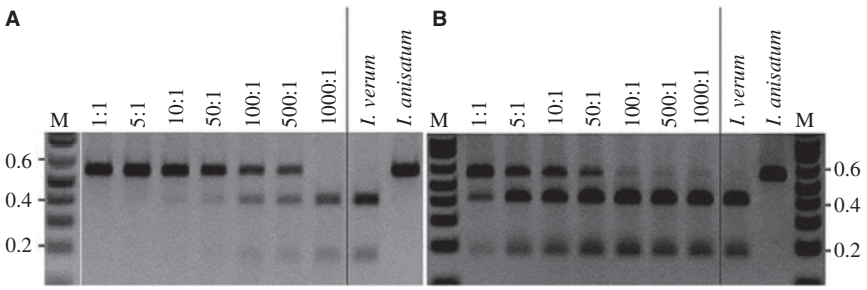


Figure 1.6 Detection of adultery of Chinese star anise (*Illicium anisatum*) with Japanese star anise (*Illicium verum*) based on PCR–RFLP of the internal transcribed spacer (ITS) region. Agarose gel image of PstI-digested PCR products. (a) From mixtures with *I. anisatum* sample 1, the detection limit was at 500:1. (b) From mixtures with *I. anisatum* sample 1073, the detection limit was at 100:1. M = molecular size standard [72].

For instance, it has been utilized to distinguish Chinese star anise from its neurotoxic adulterant Japanese star anise (Figure 1.6) [72]. Conversely, this method has been used to authenticate various species of medicinal plants.

DNA barcoding is a focused DNA Sanger sequencing technology suitable for evaluating single-ingredient herbal products. It uses small, standardized portions of the genome as species "barcodes," yet it may discover certain unrelated species.

There is a rather significant relationship between the proportion of adulterated herbal products and the kind of DNA-based technique used to examine them. The traditional DNA marker-based techniques are focused strategies meant to identify certain species, often the ones that have been labeled [74].

For these instances, Ichim (2019) considered data reporting the authenticity of 5957 commercial herbal products traded in 37 countries distributed in six populated regions, as perceived using DNA-based methods [74]. The comprehensive survey shows that a significant proportion (27%) of the herbal products marketed in the overall marketplaces are adulterated once their contents were examined against their labeled and claimed ingredient species. Adulterated herbal products are distributed across all surveyed regions and continents. The percentage of adulterated herbal products differs significantly among studied regions, in ascending order as 79, 67, 47, 33, 27, and 23% for Australia, South America, Europe, North America, Africa, and Asia, respectively. More than 100 DNA-based herbal products have been reported and successfully authenticated across nine countries. Brazil had the largest reported percentage of adulterated commercial herbal products (68%), followed by Taiwan, India, and the United States of America (29–32%), and then, far behind, Malaysia, Japan, South Korea, Thailand, and China (19–24%).

1.7.9 Nutraceuticals and Functional Foods

The field of pharmacognosy has expanded beyond traditional herbal medicines to include the development of nutraceuticals and functional foods. Nutraceuticals are bioactive compounds derived from natural sources that provide health benefits beyond basic nutrition. Functional foods are fortified or enriched with bioactive compounds to promote health and prevent diseases. Research in this area focuses on identifying and characterizing phytochemicals with specific health-promoting properties [75].

1.7.10 Sustainability and Conservation

As the demand for medicinal plants increases, there is a growing concern about the sustainability and conservation of plant resources. Pharmacognosy has placed greater emphasis on sustainable sourcing, cultivation, and harvesting practices to ensure the long-term availability of medicinal plants. Efforts are being made to promote ethical and environmentally friendly practices, including the cultivation of rare and endangered plant species [76].

1.7.11 Microbial Interactions and Co-cultivation

Researchers have started exploring the interactions between plants and microorganisms, such as endophytic as well as rhizospheric bacteria and fungi. These microorganisms can produce bioactive compounds that contribute to the medicinal properties of plants. Co-cultivation techniques, which involve growing plants and microorganisms together, have been employed to enhance the production of specific bioactive compounds and discover novel metabolites [77].

1.7.12 Biotechnological Approaches

Biotechnology plays a crucial role in pharmacognosy and phytochemistry. Genetic engineering, plant tissue culture, and metabolic engineering techniques are being utilized to enhance the production of bioactive compounds in plants. Biotechnological approaches allow for the manipulation of biosynthetic pathways, the production of rare or low-abundance compounds, and the development of plant cell culture systems for large-scale production of bioactive molecules [78].

1.7.13 Green Extraction Technology

The development of green extraction technologies aims to replace conventional extraction methods with more sustainable and environmentally friendly alternatives. Techniques such as supercritical fluid extraction, microwave-assisted extraction, and ultrasound-assisted extraction have been explored to improve extraction efficiency, reduce solvent usage, and minimize environmental impact. Green extraction methods are gaining popularity in pharmacognosy for their potential to preserve bioactivity and reduce the ecological footprint of plant extraction processes [79].

1.7.14 Big Data and Artificial Intelligence

The availability of large-scale data sets, including genomic information, chemical databases, and clinical data, has facilitated the application of big data analytics and artificial intelligence (AI) in pharmacognosy and phytochemistry. AI algorithms and machine learning techniques are

being used to mine and analyze data, predict bioactivity, optimize drug discovery processes, and identify novel drug leads from plant sources [80].

1.8 Conclusion

Pharmacognosy is the study of the use of natural products for medicinal purposes; that was the origin of pharmacy science. Ancient civilizations, such as the Egyptians, Greeks, and Chinese extensively documented the use of specific plants and plant preparations for medicinal purposes. The development of phytochemistry allows the identification of millions of new natural products as well as the standardization of the bioactive extracts using GC, HPLC, and metabolomics approaches. The recent advancements in pharmacognosy and phytochemistry are contributing to the discovery of novel therapeutic compounds, and the integration of traditional medicine with modern healthcare systems. AI algorithms and machine learning techniques will be the coming tools to predict bioactivity, optimize drug discovery processes, and allow the identification of more and more novel drug leads from plant sources.

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